

Original Article

A study to assess the correlation between biochemical indices and severity of COVID-19 infection in patients with type 2 diabetes mellitus

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COVID-19, Coronavirus Disease-2019

LDH, Lactate Dehydrogenase

CRP, C-Reactive Protein

ABSTRACT:

Objective: To describe the relationship between biochemical indices and severity of Covid-19 infection in adults with Type 2 Diabetes. **Research design & methods:** This was a single centre retrospective study conducted in a tertiary care hospital. The data of adults with Type 2 diabetes admitted with covid 19 infection between July 2020 to January 2021 was analysed. Inflammatory markers like C-reactive protein (CRP), serum ferritin and lactate dehydrogenase (LDH) levels were correlated with severity of covid based on the extent of lung involvement in CT Chest and oxygen saturation at the time of admission. The data was compared between patients who improved and those who succumbed to the illness. **Results:** 411 adults with type 2 diabetes infected with novel Corona virus were included in the study. Among patients with mild lung involvement, 99.4% had mild covid, 0.6% had moderate covid and none had severe covid whereas, in patients with severe lung involvement 84% had severe covid. The mean LDH, ferritin and CRP in survivors was 318.5 IU/L, 403.8 ng/ml, and 42.7 mg/dl respectively whereas in non survivors, the values were 36.4 IU/L, 991.6 ng/ml, and 172.8 mg/dl respectively. Comparison of CT score with disease outcome revealed 88.4% survival with mild against 7.4% with severe lung involvement. **Conclusion:** The study highlights the importance of evaluation of inflammatory biomarkers in covid patients with type 2 diabetes, which is helpful in prognostication and identification of disease severity. This will be useful in planning the treatment for better outcomes in this population.

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INTRODUCTION

Diabetes mellitus (DM) is challenging in the current context of the COVID-19 pandemic [1, 2]. The prevalence of DM in COVID-19 patients is varied across countries [3, 4]. DM interferes with the host immune system, and leads to poor outcome.

Patients with DM and other co-morbidities like hypertension, severe obesity ($\text{BMI} > 40 \text{ kg/m}^2$) are likely to be at a higher risk for mortality due to COVID-19. In some countries, there is two to three-fold mortality rate due to COVID-19 infection in diabetes patients who are admitted in intensive care units. As DM is heterogeneous among our population, it is important to determine the effect of Type 2 DM in COVID-19 patients [5, 6]. However, there is some overlap of the co morbidities like obesity, hypertension, cardiovascular disease and chronic kidney disease in patients with DM, still it is unknown whether DM independently contributes to increased risk [7]. Various studies were conducted on the effect of biochemical indices and COVID -19 severities, but there is a paucity of data regarding the effect of biochemical indices and COVID-19 infection in patients with Type 2 DM. The main aim and objective of our study was to assess the correlation between biochemical indices and severity of COVID-19 infection in Type 2 Diabetes patient.

MATERIALS AND METHODS

This was a retrospective study conducted on 411 Type 2 DM patients who were diagnosed to have COVID-19 infection. The study was conducted from July 2020 to January 2021 at Rajiv Gandhi Govt. General Hospital, Chennai, Tamil Nadu after

obtaining institutional ethical committee approval. As per the WHO recommendations [8], Type 2 DM patients who were diagnosed to have COVID-19 infection based on RT-PCR and CT scan of chest were included in this study. Patients with Type 1 DM, pregnant women, lactating mothers and patients with incomplete data were excluded from this study. After following the standard protocol for admission, these patients underwent investigations like random blood sugar (RBS) at the time of admission, complete blood count, fasting blood sugar, postprandial blood sugar, renal function test, liver function test, Creatine kinase, D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP) and serum ferritin. CT chest was done for all patients, and the disease severity was classified based on the lung involvement as mild ($< 25\%$), moderate ($25\% - 75\%$) and severe ($> 75\%$). SpO_2 level at the time of admission was recorded. Based on the COVID-19 protocol of our institution [Figure 1], COVID-19 patients were categorised into mild, moderate and severe at the time of admission. Patients with SpO_2 level between 94 to 97% in room air, CRP level 10-50 mg/l, Ferritin level between 400 to 600 ng/ml (for females 150-500 ng/ml), LDH between 220 to 300 IU/L and CT chest involvement $< 25\%$ were categorised as Mild. Patients with SpO_2 level $< 94\%$ in room air requiring oxygen, CRP level 50 to 100 mg/l, Ferritin level between 600 to 1500 ng/ml (for females 500 to 1000 ng/ml), LDH between 300 to 500 IU/L and CT chest involvement of 25 to 75 % were categorised as moderate and patients with SpO_2 level $< 90\%$ in room air requiring oxygen, CRP level $> 100 \text{ mg/l}$, Ferritin level between $> 1500 \text{ ng/ml}$ (for

females > 1000 ng/ml), LDH between > 500 IU/L and CT chest involvement of 75 % to 100 % were categorised as severe. Patients were treated with oxygen therapy where-ever required, low molecular weight heparin (LMWH), dexamethasone, Remdesivir/Tocilizumab and other supportive measures based on the severity of COVID-19. Statistical analysis was done using ANOVA test for comparison of quantitative variable and categorical variable, while chi-square test was used to test the significance level between categorical variables.

RESULT

Among the study population of 411 patients, 63.26% (260) were males and 36.74% (150) were females. On comparing the inflammatory parameters with disease severity [Table 1], the mean value of LDH was 318.6 IU/L in mild disease, 507.4 in moderate and 745.2 in severe cases. For serum Ferritin, the mean value was 373 for mild, 684.6 for moderate and 1342 for severe cases. The mean CRP level value was 49.6 in mild, 105.5 in moderate and 222.3 in severe cases. On comparing SpO₂, the mean value was 97.3% in mild, 92.9% in moderate and 81.1% in severe cases. On comparing CT score with the disease severity [Table 2], among patients with mild lung involvement 99.4% (163) patients had mild, 0.6% (1) patient had moderate and none had severe Covid-19. When lung involvement was moderate 15.8% (24) patients had mild, 73% (111) patients had moderate and 11.2% (17) patients had severe Covid-19. Among patients with severe lung involvement 4.3% (4) had mild, 11.7% (11) had moderate and 84% (79) had severe Covid-19. On comparing the inflammatory

parameters with disease outcome [Table 3], the mean LDH value was 318.5 IU/L in patients who improved and 636.4 IU/L in patients who died. The mean value of serum ferritin was 403.8 ng/ml in survivors and 991.6 ng/ml in non-survivors. The mean value of CRP was 42.7 mg/dl in survivors and 172.8 mg/dl in non survivors. Mean SpO₂ was 96.1% in survivors and 88.2 % among non-survivors. On comparing the CT score with the disease outcome [Table 4], among patients with mild involvement 88.4% (145) improved and 11.6% (19) died. With moderate lung involvement 36.8% (56) survived and 63.2% (96) died. Severe lung involvement was seen in 7.4% (77) survivors and 92.6 % (87) of patients who died due to COVID-19 and its complication.

DISCUSSION

A relationship between diabetes and infections has been clinically recognized. Infections like influenza and pneumonia are often common and serious in older people with Type 2 Diabetes mellitus.

Nevertheless, the evidence remains controversial that diabetes itself indeed increases susceptibility and impacts outcomes from infections [9, 10].

Diabetes is among the most frequent reported co-morbidities in patients with COVID-19 infection [11]. However, DM remains a risk factor for developing severe and critical forms of COVID-19, requiring admission to an ICU or use of invasive mechanical ventilation, with higher mortality rates than euglycaemic individuals. The characteristics of diabetes patients at risk for developing severe and critical forms of COVID-19 are under investigation

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COVID 19 TREATMENT PROTOCOL

PARAMETERS	SEVERE			MODERATE		MILD	ASYMPTOMATIC
Spo2*	<90% on RA requiring O2			<94% in Room air requiring O2		94-97% in RA	>97% in RA
RR	>30			24-30		<24	with normal RR

NLR	>7	>5	>3.13	IF INVESTIGATIONS ARE WITHIN LIMITS 1. <55 YEARS WITH NO COMORBIDITY REFER TO COVID CARE CENTER 2. >55 YEARS WITH COMORBIDITY REFER TO COVID HEALTH CENTER
CRP (mg/l)	>100	50-100	10-50	
FERRITIN(ng/ml)**	>1500 (F - >1000)	600-1500 (F- 500-1000)	400-600 (F- 150-500)	
LDH (IU/L)	>500	300-500	220-300	
D-DIMER mic/ml)	>1.0	0.5-1.0	<0.5	
IL6(pg/ml)	>100	20 - 100	8-20	
CT CHEST	75%-100%	25-75%	< 25%	

SPO2 TARGET	90-94%		94-96%		94-96%	O2 FLOW CHART IN ANNEXURE I
OXYGEN DEVICES	NRM	8-15 LTS	MASK	5-8 LTS	MONITOR SPO2 Q4H, IF SPO2 DROPS <94% START 3-5 LTS VIA MASK	
	HFNO	30-70 LTS	NRM	8- 15 LTS		
	CPAP	3-12 CM H2O				

DRUGS	SEVERE			MODERATE		MILD		
MEDICINE	Dose	Freq	Days	MEDICINE	Dose	MEDICINE (oral)	Dose	Frequency
ENOXAPARIN**	40 mg	BD	7-10	ENOXAPARIN**	40 MG	PARACETAMOL	500 mg	SOS
DEXA	8 mg	OD	7	DEXA	8 mg (3-5 days)	AZITHROMYCIN	500 mg ST	250 for 4 days OD
CEFTRIAZONE	2 gm	OD	5-7	CEFTRIAZONE	2GMS	VIT C	500 mg	OD
VIT C	1 gm	OD	5	PANTAPRAZOLE	40 MG	ZINC (elemental)	50 mg	OD
THIAMINE	200mg	OD	5	REMDESIVIR****		PANTAPRAZOLE	40 mg	OD
PANTAPRAZOLE	40 mg	OD	5	TOZULICIMAB****	400 mg(1dose) 2 nd Dose ±	ADEQUATE HYDRATION ORALLY ENCOURAGED		
TOZULICIMAB	400 mg	2 doses 12 hrs apart						
REMDESIVIR								

LAB TESTS	SEVERE	MODERATE	MILD
CBC	48 HRS	48 HRS	48 HRS
RLE	48 HRS	48-72 HRS	72 HRS
COVID PROFILE	48 HRS	48- 72 HRS	72 HRS
D-DIMER	72 HRS	48 HRS	72 HRS
PROCALCITONIN	72 HRS /SOS	SOS	-
LACTATE	72 HRS/SOS	SOS	-
IL6	-	24	-
CXR - BED SIDE	CLINICALLY INDICATED	IF CLINICALLY INDICATED	IF CLINICALLY INDICATED

OTHERS LIKE TROPONIN, pro BNP IF CLINICALLY INDICATED

DISCHARGE CRITERIA	1. Repeat swab negative 2. Without o2 support for 4 days	1.STABLE AND WITH OUT OXYGEN SUPPORT FOR 4 DAYS	IF STABLE REFER TO COVID HEALTH CENTRE AFTER 3 DAYS OF MONITORING FOR FURTHER OBSERVATION
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ARDS: New or worsening respiratory symptoms unrelated to cardiac or other causes with PEEP of 5MM HG 1. MILD: P/F<300 or SPO2/FIO2 <315 2.MODERATE: P/F <200 or SPO2/FIO2 235. 3.SEVERE: P/F <100 or SPO2/FIO2:<150 if HFNO and CPAP fails treat with low tidal volume 6 ml/kg RR 20-35/mt with plateau pressure around 30. Prone ventilation advised in refractory hypoxemia

Acute life threatening organ dysfunction like decreased urine output, acidosis, high lactate, altered LFT(sepsis)and hypotension despite volume resuscitation requiring vasopressors (septic shock) with high lactate level and procalcitonin should be treated accordingly by escalating antibiotics, careful fluid therapy.

GENERAL MEASURES: 1.ECG for all patients. 2. Strict diabetic Control as per guidelines issued in Annexure III. 3. Advise to get oxygenated in prone position with the pillow in longitudinal position.(ANNEXURE II) 4.High protein diet 5.Maintain adequate hydration fluids NS after clinical assessment of volume status 6.Completebedrest 7. ABG as and when required.

*FOR COPD: SPO2 OF 2-4% lower values are acceptable *FERRITIN **LMWH. 1.For enoxaparin if increased renal parameters once daily can be given 2.For daltaparin 5000 units can be given once daily 3.CI: plt < 25000, evidence of active bleeding ***TOZULICIMAB.1.400 mg diluted in 100 ml ns given over 1 hour 2. Repeat dose after 12 hours CI: immunosuppressive states, PLHA, active bacterial fungal infections. (Start if 3 out of five markers present)****REMDESIVIR: (better, if started early in the course of illness) 1. 200 mg in 250 normal saline over 4 hours on first day 2. 100 mg in 100ml NS infusion from 2nd day onwards for 5 days 3. If on ventilatory support continue for another 5 days 4. To monitor RLE every 48- 72 hrs. : contraindications 1. ALT> 5 times 2. Pregnancy, Lactation 3. Caution in Sr. Creatinine clearance <30ml/mt

Figure 1 showing the Institutional protocol for COVID-19 infection.

Parameter	Disease severity						P value
	Mild (n=191)		Moderate (n=123)		Severe (n=96)		
	Mean	SD	Mean	SD	Mean	SD	
LDH (IU/L)	318.6	153.4	507.4	239.3	745.2	544.4	0.0001
Ferritin ng/ml	373	384.1	684.6	587	1342	1536.1	0.0001
CRP (mg/dl)	49.6	81.9	105.5	85.7	222.3	211.2	0.0001
SpO2 (%)	97.3	1.3	92.9	1.9	81.1	13.5	0.0001

Table 1 Comparison of serum markers and SpO₂ with the disease severity in covid-19 patients

CT score	Disease severity			P value
	Mild (%)	Moderate (%)	Severe (%)	
Mild (25%)	163 (99.4%)	1 (0.6%)	0	0.0001
Moderate (25-75%)	24 (15.8%)	111 (73%)	17 (11.2%)	
Severe (75-100%)	4 (4.3%)	11 (11.7%)	79 (84%)	

Table 2 showing comparison of CT score with the disease severity in covid-19 patients

Parameter	Disease outcome				P value
	Discharged (n=208)		Death (n=202)		
	Mean	SD	Mean	SD	
LDH	318.5	140.6	636.4	428.9	0.0001
Ferritin	403.8	413.8	991.6	1187.4	0.0001
CRP	42.7	56	172.8	171.8	0.0001
SpO ₂	96.1	2.7	88.2	11.6	0.0001

Table 3 comparison of serum markers and SpO₂ with the disease outcome in covid-19 patients

CT findings	Disease outcome		P value
	Discharge (%)	Death (%)	
Mild 25%	145 (88.4%)	19 (11.6%)	0.0001
Moderate (25-75%)	56 (36.8%)	96 (63.2%)	
Severe (75-100%)	7 (7.4%)	87 (92.6%)	

Table 4. Comparison of CT findings with the disease outcome in COVID-19 patients

[12, 13]. However, the potential mechanisms that may increase the severity and complications for COVID-19 in diabetes are postulated to be higher affinity cellular binding and efficient virus entry, decreased viral clearance, diminished T-cell function, increased susceptibility to hyper inflammation and cytokine storm syndrome and presence of cardiovascular disease [14]. In vitro studies have shown that pulmonary epithelial cell exposure to high glucose concentrations significantly increases influenza virus infection and replication, indicating that hyperglycaemia may enhance viral replication [15].

In our study, the mean LDH value significantly increases from mild cases to severe cases. The results of our study were similar with study conducted by Jialin xiang et al [16], which showed a significant increase of LDH values as the diseases progressed from mild to severe. That study also showed that the serum CRP levels had no significant difference in severe and mild cases; however, the overall level of CRP increased suggesting that it could be sensitive to SARS-CoV-2. In our study also we observed an overall increase in CRP levels according to the severity of the disease. Study conducted by Xu L et al [17] showed LDH level is associated with severe and critical illness and their levels likely indicate adverse

outcomes. A similar result was seen in our study where the mean LDH level was significantly higher in patients who died of COVID-19 than compared to discharged patients.

Serum ferritin level was found to be significantly higher in severe cases of COVID-19 than compared to mild and moderate cases. The result of our study was similar with study conducted by Ji M et al [18]. Based on the above observation serum ferritin may be considered as one of the prognostic markers in COVID-19 patients.

Study conducted by Chen et al [19], showed CRP, Ferritin, LDH, ALT was significantly higher in severe cases than mild and moderate cases. In our study ALT was not estimated but other blood parameters were found to be elevated in severe cases with statistical significance. Study conducted by Zhang B et al [20] showed that serial measurements of these markers can also be used to predict disease course, severity and mortality.

Comparing the above study results, we found that the biomarkers were significantly elevated in non-survivors compared to survivors in discharged patients [Table 4]. However, the above study was compared among normal patients with COVID-19 infection. In our study, we had a similar result among Type 2 diabetes patients and the various

biochemical parameters were found to be significantly increased.

On comparing CT score with the disease severity, we found that the CT score increased with increasing disease severity. CT score was significantly increased in patients who died of COVID-19 than those who survived as shown in a study conducted by Hu Y et al [21], concluded that severity score of lung involvement in patients who died from COVID-19 was significantly greater than that in patients with mild to moderate disease.

CONCLUSIONS

Biochemical markers play an important role in understanding the severity and prognosis of COVID-19 infection. Serum markers like LDH and ferritin are significantly raised in severe and critically ill patients and their increased levels indicate an adverse outcome. CRP also appears to be a sensitive marker for COVID-19 infection severity. Significant elevation in all these markers carries a higher chance of severe disease and mortality in diabetes patients. CT findings also correlate with the disease severity and mortality.

Hence, we conclude that, inflammatory biochemical parameters are useful in identifying the severity of COVID-19 infection in individuals with diabetes. Significant increase in these biochemical markers along with CT findings can be useful in assessing the prognosis of patients with COVID-19. Serial monitoring of inflammatory markers will be helpful in identifying the progression of disease severity and accordingly treatment can be targeted to have a better outcome in patients with COVID-19.

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Geethanjali J: Investigation, Analysis, Preparation of original draft.

Pushpa Saravanan: Analysis, Supervision, Review and Editing.

Vasuki R: Supervision, Review and Validation.

Dharmarajan P: Conceptualization, Methodology, Editing.

Periyandavar I: Project Administration, Editing.

Declaration of Competing Interest

None

Peer-Review

The manuscript has been reviewed by

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Supplementary material

Not applicable

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